Night-shift work and breast and prostate cancer risk: updating the evidence from epidemiological studies

Trabajo nocturno por turnos y el riesgo de cáncer de mama y próstata: actualizando la evidencia a partir de estudios epidemiológicos

doi.org/10.23938/ASSN.0307

E. Salamanca-Fernández[1,2,3], M. Rodríguez-Barranco[1,2,3], M. Guevara[3,4], E. Ardanaz[3,4], A. Olry de Labry Lima[1,2,3], M.J. Sánchez[1,2,3]

ABSTRACT

It has been hypothesized that circadian disruption is related to higher cancer risk. Since the International Agency for Research on Cancer classified shift work involving circadian disruption as *probably carcinogenic to humans* (Group 2A), multiple studies have been conducted to test this hypothesis. The aim of this systematic review was to summarize the findings and evaluate the quality of existing epidemiological studies (case-control and cohort studies) on the relationship between night-shift work and breast and prostate cancer risk.

Thirty-three epidemiological studies investigating the relationship between night-shift work and breast (n = 26) or prostate (n = 8) cancer risk were included (one paper included both sites). The Newcastle-Ottawa Scale for the quality of non-randomized studies was used to assess the risk of bias of the publications. The studies included were heterogeneous regarding population (general population, nurses working in rotating shifts, and other) and measurement of exposure to night-shift work (ever vs. never exposure, short vs. long-term, rotating vs. permanent) and, thus, a diversity of outcomes were observed even within the same type of cancer. In summary, 62.5% works found some type of association between night-shift work and increased risk of cancer, for both breast and prostate. The risk of bias scored an average of 7.5 over 9 stars. Due to the limitations inherent in these studies, the evidence of a possible association between night-shift work and breast or prostate cancer risk remains uncertain and more studies providing greater control of exposure and confounding factors are required. Despite the lack of conclusive evidence, application of the precautionary principle seems advisable.

Keywords. Breast cancer. Prostate cancer. Shift work. Circadian disruption. Light at night.

RESUMEN

Se ha formulado la hipótesis de que la disrupción circadiana está relacionada con un mayor riesgo de cáncer. Desde que la Agencia Internacional de Investigación sobre el Cáncer clasificó la disrupción circadiana asociada al trabajo por turnos como "probablemente carcinógeno para los humanos" (Grupo 2A) se han llevado a cabo numerosos estudios para confirmar o rechazar esta hipótesis. Por esa razón, el objetivo de esta revisión sistemática fue analizar la posible asociación entre el trabajo nocturno por turnos y el riesgo de cáncer de mama o próstata.

Se incluyeron treinta y tres estudios epidemiológicos sobre la relación entre el riesgo de padecer cáncer de mama (n = 26) o próstata (n = 8) y el trabajo nocturno; un estudio evaluó ambas localizaciones. El riesgo de sesgo de los artículos se evaluó mediante la escala Newcastle-Ottawa. Los estudios incluidos en esta revisión fueron heterogéneos respecto a población incluida (población general, enfermeras a turnos, y otros), medida de la exposición a trabajo nocturno (siempre vs nunca, a corto vs largo plazo, a turnos o fijo) y, por tanto, los hallazgos fueron variados incluso para el mismo tipo de cáncer. En resumen, un 62,5% de los estudios encontraron asociación entre el trabajo nocturno y el riesgo aumentado de padecer cáncer, tanto de mama como de próstata. El riesgo de sesgo medio fue de 7,5 estrellas sobre 9. Debido a las limitaciones inherentes a estos estudios, la evidencia de una posible asociación entre el trabajo nocturno y el riesgo de cáncer de mama o próstata sigue siendo incierta, por lo que se requieren más estudios epidemiológicos con mayor control de la exposición y de los factores de confusión. No obstante, parece aconsejable la aplicación del principio de precaución.

Palabras clave. Cáncer de mama. Cáncer de próstata. Trabajo por turnos. Disrupción circadiana. Exposición a luz durante la noche.

An. Sist. Sanit. Navar. 2018; 41 (2): 211-226

1. Andalusian School of Public Health (EASP). Granada. Spain
2. Instituto de Investigación Biosanitaria ibs.GRANADA. University Hospitals of Granada/University of Granada. Granada. Spain
3. CIBER Epidemiology and Public Health (CIBERESP). Spain
4. Instituto de Salud Pública de Navarra, IdiSNA. Pamplona. Spain

Corresponding:
Miguel Rodríguez-Barranco
Andalusian School of Public Health (EASP)
Campus Universitario de Cartuja
C/Cuesta del Observatorio 4
18080 Granada_Spain
E-mail: miguel.rodriguez.barranco.easp@juntadeandalucia.es

Recepción: 15/11/2017
Aceptación provisional: 12/04/2018
Aceptación definitiva: 19/06/2018

INTRODUCCIÓN

Approximately 20% of the working population in Europe and North America works in shifts[1]. Shift work is most frequent in the transport sector, factories, and emergency services (i.e. hospitals, primary care, law enforcement, fire-fighting, etc.). Shift- and night-time work is increasing in modern societies. However, people who work at night tend to sleep less, are exposed to artificial light during night hours, and stay awake when they would normally be resting.

At the same time, the burden of cancer is growing worldwide[2] and breast and prostate cancer have the greatest incidence in women and men, respectively[3,4]. Risk factors responsible for the growing rate of cancer incidence are multiple and heterogeneous. It is well known that the occurrence of cancer cannot be attributed solely to genetic factors. In fact, research shows that about half of the global cancer burden is due to modifiable factors (e.g., obesity, diet, sedentary lifestyle, endocrine disrupting chemicals, etc) and is hence potentially preventable[5,6].

Research has shown that animal exposed to light at night (LAN) showed increased mammary carcinogenesis[7-9]. Although there is less evidence in humans[10,11], various studies suggest that female night-shift workers have an increased risk of breast cancer[12,13].

Based on evidence (mostly from studies on animals), the International Agency for Research on Cancer (IARC) published a report in 2007 stating that shift work involving circadian disruption is "probably carcinogenic to humans"[11] (Group 2A). Two years after the IARC report, Denmark was obliged to pay compensation to thirty-eight long-term female night-shift workers who had developed breast cancer[14]. However, the evidence for the association between night-shift work and cancer risk was uncertain.

According to the IARC statement, night-shift work could negatively affect human health as it may increase the risk of developing cancer. In mammals, exposure to LAN disrupts the circadian clock that coordinates biology and behaviour with daily environmental changes in the day-night cycle[15]. Exposure to artificial light occurs through the retina, and this decreases melatonin production[16]. Given that melatonin protects animals from cancer[17-20] and inhibits tumour growth in human cancer cells[21,22], it is believed that it has oncostatic properties, including possible anti-estrogenic and anti-aromatase activity, and also that decreased melatonin production may lead to increased oestrogen production[23,24].

Circadian rhythm is a mechanism related to the cycle of light and dark influencing sleep, body temperature and hormone secretion[14,25-27], and it is linked to the endocrine system, as hypothalamus regulates the production of melatonin by the pineal gland. Circadian disruption takes place when environmental factors, such as LAN, interact with the circadian pacemarker located in the suprachiasmatic nucleus of the hypothalamus. Since the highest levels of melatonin are produced along the night[28], exposure to LAN alters its natural release.

There have been several systematic reviews and meta-analyses on breast cancer and its possible relation to both night-shift work and circadian disruption, but the evidence provided remains inconclusive[12,29,30] and they did not included the latest studies. On the other hand, fewer studies have focused on prostate cancer and night-shift work[31]. We decided to include both breast and prostate cancer in order to study the most frequent hormone-related cancers widening the scope of this review. Accordingly, the objective of this systematic review was to analyze the potential link between night-shift work and breast or prostate cancer risk.

METHODS

Systematic review of studies assessing the relationship between night-shift work and risk of breast or prostate cancer. A comprehensive search of works published up to October 2017 was undertaken through CINAHL, Embase, Scopus, Web of Knowledge, and PubMed databases. The search strategy used thesauri as well as the following keywords: (*shift work*, Shift Work Schedule [Mesh] *OR night-work OR rotating*

shift OR evening shift OR night time shift OR night-shift work OR circadian disrupt OR circadian disruption OR circadian rhythm) AND (melatonin [Mesh], breast [Mesh] *cancer*, prostate [Mesh] *cancer*, neoplasms [Mesh]). Cross-references were reviewed by reading systematic reviews and meta-analyses to locate studies not included in the results.

The inclusion criteria were: epidemiological studies (case-control and cohort studies) performed in humans, independently of age or sex, published after the year 2000, assessing the relationship between occupation-related exposure (lack of night-time sleep related with circadian disruption) and breast or prostate cancer. Studies regarding lack of sleep due to factors other than occupation and exposure to LAN were excluded, as also were studies about circadian disruption due to stress, jet lag, or non-occupational factors.

The Newcastle-Ottawa Scale (NOS) for the quality of non-randomized studies[32] was used to assess the risk of bias of the included studies. This scale is recommended by the Cochrane Collaboration and comprises eight questions grouped in three domains: selection, comparability, and exposure (case-control) or outcome (cohort), and scored between zero and nine stars.

The selection of studies was independently performed by two reviewers (ESF and AOL) and any discrepancies were resolved by a third reviewer (MRB); all of them piloted 50 publications in order to agree on basic concepts and to refine the selection criteria. Title and abstract of each published study were checked against the inclusion criteria; full text of the remaining studies was assessed. The open-source reference management software Mendeley was used. A form for data extraction was created to record bibliographic information as well as the general characteristics of the studies, such as population, effect size, exposure, and adjusted variables.

RESULTS

Our search produced 958 results for night-shift work and cancer. A total of 841 studies were excluded in the first phase alter reading of title and abstract. Further 88 publications were excluded, and four additional publications were included after searching cross-references (Fig. 1). Finally, a total of 33 epidemiological studies[33-65] met all the inclusion criteria, including 16 cohort studies and 17 case-control studies, and were classified into two groups: breast cancer (twenty-six studies) and prostate cancer (eight studies); one study reported on both cancer sites (Table 1).

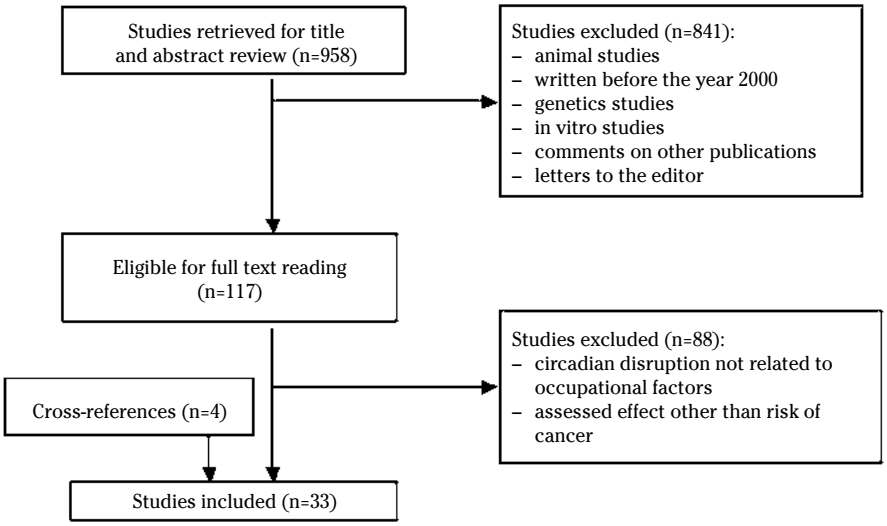

Figure 1. Flow diagram of the search and selection of reviews.

Table 1. Characteristics of works studying night-shift work and risk of breast or prostate cancer included in this review

Characteristics	N	%
Cancer site[a]		
Breast	26	76.5
Prostate	8	23.5
Study design		
Cohort	16	48.5
Case-control	17	51.5
Quality score[b]		
6	3	9.1
7	13	39.4
8	10	30.3
9	7	21.2
Population		
General population	15	45.5
Nurses	7	21.2
Members of the Armed Forces	1	3.0
Twins database	3	9.1
Workers in other sectors	7	21.2

[a:] one study included both cancer sites; [b:] number of stars scored following the Newcastle-Ottawa Scale.

Regarding epidemiological design, 48.5% of works were cohort studies and 51.5% were case-control (Table 1). Most studies were conducted on samples drawn from the general population (45.5%) and 21.2% focused solely on nurses. Table 2 shows the main characteristics of each study, namely: population sample, study type, cancer type and exposure measurement of night-shift work.

Study populations were heterogeneous also in terms of occupation (Table 1). Some of the publications reported results from the female cohort of the Nurses' Health Study (NHS), which is composed of the NHS or NHSII, depending on the time of recruitment. The NHS is a research study on the risk factors for major chronic diseases in women in the USA. It started in 1976 with 121,701 female nurses between 30-55 years of age. In contrast, the NHSII began in 1989 with 116,671 female registered nurses, 25-42 years of age. From enrolment, participants in both cohorts have completed follow-up questionnaires at two-year intervals with regard to their health status and medical history. Other selected publications were based on studies such as the Shanghai textile bureau, GENICA, Swedish Registry, the Norwegian Board of Health, CECILE study, WOLF longitudinal study, MCC-Spain, Million Women Study, Swedish twin registry, EPIC-Oxford, and UK Biobank.

The selected studies were heterogeneous about exposure measurements due to differences in night-shift work exposure and assessment methods (Table 2). Some studies compared an *ever exposure* to a *never exposure* to night-shift work[61], while other[47,54,59] discriminate between short and long-term night-shift work without agreeing in the concept of short-term; moreover, type of shift work was assessed: rotating[33], permanent night-shifts[63] or both[59]. In addition, most studies gathered data by means of questionnaires while other did via personal interview or by extrapolation[59] (Table 2).

Table 2. Characteristics of the selected studies on breast cancer or prostate cancer and night-shift work

Year	Study type (N) Population	Cases Effect[a]	Exposure definition and assessment	Adjusted variables
Breast cancer				
Davis *et al* (2001)[64]	Case-control $N_{controls}$ = 793 Women from GP	N_{cases} = 813 OR = 1.14 (1.01-1.28)	Number of nights/week, continuously - Interview	Parity, breast cancer in mother and/or sister, OC use (ever), and discontinued use of HRP <5 years ago
Hansen *et al* (2001)[48]	Case-control $N_{controls}$ = 7,035 Women from GP	N_{cases} 7,035 OR = 1.5 (1.3-1.7)	≥6 months in trades with ≥60% nigh-work - Interview	Socio-economic status, age at the birth of first and last child, and number of children
Schernhammer *et al* (2001)[40]	Cohort N = 78,562 Nurses NHS	N = 2,441 RR = 1.36 (1.04-1.78)	≥30 years night-shift work - Interview	Age, menarche before age 12, parity, age at first birth, first-degree family history of breast cancer, history of benign breast disease, ever use OC, postmenopausal in 1988, age at menopause, current PMH and BMI, BMI at age 18, menopause, alcohol consumption, socioeconomic status, education
Schernhammer *et al* (2005)[43]	Nested case-control $N_{controls}$ = 291 Nurses NHSII	N_{cases} = 147 OR = 0.59 (0.36-0.97)	Number of nights in 2 weeks before urine collection; lifetime history of night-work - Self-administered questionnaire, biomarkers (melatonin levels)	Age, menopausal status, age at menarche, number of births, family history of breast cancer, BMI, alcohol, history of benign breast disease, current antidepressant use, worked night-shift ≥1 during the 2 weeks before urine collection, never worked night-shift, months worked on rotating night-shifts
O'Leary *et al* (2006)[42]	Case-control $N_{controls}$ = 509 Women from GP	N_{cases} = 487 OR = 0.32 (0.13-0.81)	≥8 years night-shift work - Interview	Age, ever used alcohol, history of benign breast disease, education, ever used hormone replacement therapy, ever used OC, family history of breast cancer, history of fertility problems, ever lactated, ever had a mammogram, reproductive history, ethnicity, religion, total household income before taxes in the last year
Schernhammer *et al* (2006) [37]	Cohort N = 115,022 Nurses NHS	N = 1,352 RR = 1.79 (1.06-3.01)	≥20 years night-shift work - Interview	Age, family history of breast cancer, BMI, age at menarche, history of benign breast disease, ever used OC; age at first birth, parity, alcohol consumption, premenopausal, current smoker
Lie *et al* (2006) [46]	Nested case-control $N_{controls}$ = 2,143 Nurses	N_{cases} = 537 OR = 2.21 (1.10-4.45)	≥30 years night-shift work - Norwegian Board of Health's registry of nurses	Years with night-work, total employment time as a nurse, year of birth of nurses, age at graduation /first job, age at diagnosis of case, nulliparous, number of children, age at first birth
Pronk *et al* (2010) [38]	Cohort N = 73,049 Women from GP	N = 717 HR = 0.8 (0.5-1.2)	>17 years night-shift work - Self-administered questionnaire	Age at cohort entry, breast cancer in first-degree relative, education, premenopausal, age at menarche, age at first live birth, no. of pregnancies, BMI, total caloric intake, occupational physical activity

Year	Study type (N) Population	Cases Effect[a]	Exposure definition and assessment	Adjusted variables
Pesch *et al* (2010) [65]	Case-control $N_{controls}$ = 57 Women from GP	N_{cases} = 56 OR = 2.48 (0.62-9.99)	≥20 years night-shift work - Interview	Age, menopausal status, education, parity, age at first birth, OC, hormone therapy, cigarette smoking, BMI, breast cancer in mother/sisters, no. of mammograms
Lie *et al* (2011) [49]	Nested Case-control $N_{controls}$ = 895 Nurses	N_{cases} = 699 OR = 1.8 (1.1-2.8)	≥5 years with ≥6 consecutive night-shifts - Interview	Age at stop time, menarche before age 12 years, age at menarche, years, nulliparous, no. of children, age at first birth, first degree family history of breast cancer, ever use of OC or IUD, postmenopausal at stop time, age at menopause, BMI, recent hormonal treatment, alcohol consumption at stop time, ever smoked, daily exposure to x-rays
Hansen and Stevens (2012) [61]	Nested case-control $N_{controls}$ = 1,035 Nurses	N_{cases} = 267 OR = 2.1 (1.3-3.2)	≥20 years night-shift work - Interview and self-administered questionnaire	Age, length of work, marital status, years of schooling, occupational history, tobacco and alcohol drinking pattern, physical activity, reproductive history, use of contraceptives, use of HRT, breast cancer in mother and/or sister, BMI at age 20 and at the interview, significant weight fluctuations since age 20, hours of sleep at the time of interview and 10 years previously
Hansen and Lassen (2012) [63]	Nested case-control $N_{controls}$ = 899 Military women	N cases = 218 OR = 2.1 (1.0-4.5)	≥ 15 years night-shift work - Self-administered questionnaire	Age, BMI, smoking, alcohol drinking, sun exposure habits, reproductive history, OC and HRT use, physical activity at work, occupational exposure to radar or electromagnetic fields, occasional sunbathing frequency, educational level, and diurnal preference
Fritschi *et al* (2013) [44]	Case-control $N_{controls}$ = 1,789 Women from GP	N_{cases} = 1,205 OR = 1.02 (0.71-1.45)	>20 years night-shift work - Self-administered questionnaire and telephone interview	Age group, menopausal status, socioeconomic and remoteness score, education, country of birth, family history of breast cancer, number of children, breastfeeding, alcohol intake, physical activity, BMI, circadian type, circadian rhythm, circadian flexibility
Grundy *et al* (2013) [62]	Case-control $N_{controls}$ = 1,179 Women from GP	N_{cases} = 1,134 OR = 2.21 (1.14-4.31)	≥30 years shift work - Self-administered questionnaire, telephone interview, and medical records	Age, BMI, ethnicity, household income, education, menopausal status, medication use, number of years of NSAID, OC, antidepressant and HRT use, reproductive history, lifestyle characteristics, lifetime alcohol consumption
Rabstein *et al* (2013) [35]	Case-control $N_{controls}$ = 892 Women from GP	N_{cases} = 827 OR = 4.73 (1.22-8.36)	≥20 years night-shift work - Interview and biomarkers: determination of ER expression	Age, menopausal status, education, breast cancer in mother or sister, parity, age at first birth, duration of OC and HRT use, BMI, smoking, status of mammograms until two years before interview, and lifetime breastfeeding

Year	Study type (N) Population	Cases Effect[a]	Exposure definition and assessment	Adjusted variables
Knutsson *et al* (2013)[60].	Cohort N = 4,036 Women from GP	N = 94 HR = 2.02 (1.03-3.95)	Shift with night-versus day - Self-administered questionnaire and medical examination	Age, education, given birth, smokers, alcohol intake, BMI, waist-hip ratio, passed menopause, OC use, hormones other than contraceptives
Menegaux *et al* (2013) [47]	Case-control $N_{controls}$ = 1,317 Women from GP	N_{cases} = 1,232 OR = 1.27 (0.99-1.64)	Ever worked at night - Self-administered questionnaire	Demographic and socioeconomic characteristics, reproduction, medical history, family history of cancer, diet, lifestyle factors, residential and occupational history over the lifetime
Koppes *et al.* (2014) [57]	Cohort N = 285,723 Women from GP	N = 2,531 HR = 1.04 (0.85-1.27)	Occasional and regular night-work - Computer assisted personal interview	Age, origin, children in the household, education, occupational group, contractual working hours, and job tenure
Åkerstedt *et al* (2015) [36]	Cohort N = 13,656 Women from the Swedish Twin Registry	N = 463 HR = 1.77 (1.03-3.04)	>20 years night-shift work - Interview	Educational level, tobacco use, alcohol use, physical activity, body mass, have children, coffee use, previous cancer, menopause, use of hormones, including OC
Wang *et al* (2015) [39]	Case-control $N_{controls}$ = 742 Women from GP	N_{cases} = 712 OR = 1.34 (1.05-1.72)	Ever night-work - Interview	Age, education, BMI, marital status, age at menarche, menopausal status, age at menopause, parity, physical activity, breast-feeding, family history of breast cancer
Li *et al* (2015) [41]	Nested case-cohort N_{cohort} = 4,780 Textile workers	N_{cases} = 1,709 HR = 0.88 (0.74-1.05)	>27.67 years night-shift work - Self-administered questionnaire and interview	Age, age at beginning of follow up, duration of follow up, years of employment in STIB, average number of jobs held, years doing shift work
Papantoniou *et al* (2016) [55]	Case-control $N_{controls}$ = 1,778 Women from GP	N_{cases} = 1,708 OR = 1.18 (0.97-1.43)	Ever night-work - Interview	Age, family history of breast cancer, menopause status, BMI, alcohol consumption at the age of 30-40, use of OC, education, marital status, tobacco smoking, physical activity, diet habits
Travis *et al* (2016) [54]	a) Million Women Study cohort N = 522,246 b) EPIC-Oxford cohort N = 22,559 c) UK Biobank cohort N = 251,045 Women from GP	a) N = 673 RR = 1.00 (0.92-1.08) b) N = 28 RR = 1.07 (0.71-1.62) c) N = 67 RR = 0.78 (0.61-1.00)	Any vs. no night-shift - Questionnaire	Socioeconomic status, age at menarche, parity and age at first birth, body mass index, alcohol intake, smoking, strenuous physical activity, family history of breast cancer, living with a partner, use of OC, and RHT
Wegrzyn *et al* (2017) [33]	Nurses cohort a) NHSI N = 78,516 b) NHSII N = 114,559	N = 9,541 a) HR = 0.95 (0.77-1.17) b) HR = 2.15 (1.23-3.73)	Long term rotating shift work - Interview	Age, family history of breast cancer; BMI, age at menarche, history of benign breast disease, ever used OC; age at first birth, parity, alcohol consumption, premenopausal, current smokers

Year	Study type (N) Population	Cases Effect[a]	Exposure definition and assessment	Adjusted variables
Vistisen *et al* (2017) [34]	Cohort N = 155,540 Public sector female workers	N = 1,245 RR = 0.90 (0.80-1.01)	Ever working night-shifts - Danish working database	Age, age at first child, parity, family history of breast or ovarian cancer, sex hormones, medications related to alcoholism, family educational level, mammography screening
Schwartzbaum *et al* (2007) [59]	Cohort N = 1,148,661 Women working at least half time	SIR = 0.94 (0.74-1.18)	Extrapolation from the ULF - Interview	Age, socioeconomic status, occupational position, county of residence
Prostate cancer				
Schwartzbaum *et al* (2007) [59]	Cohort N = 2,102,126 Men working at least half time	SIR = 1,04 (0.99-1.10)	Extrapolation from the ULF - Interview	Age, socioeconomic status, occupational position, county of residence
Kubo *et al* (2006) [52]	Cohort N = 14,052 Male workers	N = 31 RR = 3.0 (1.2-7.3) RR = 1.7 (0.5-5.9)	Rotating-shift workers. Fixed nights - Self-administered questionnaire	Age, family history of prostate cancer, study area surveyed, body mass index, smoking, alcohol drinking, job type, physical activity at work, workplace, perceived stress, educational level, marital status
Kubo *et al* (2011) [51]	Cohort N = 4,995 Male workers	N = 17 OR = 1.79 (0.57-5.68)	Mean = 25.3 years of shift work - Self-administered questionnaire	BMI, alcohol intake, smoking, exercise, marriage status
Parent *et al* (2012) [58]	Cohort N = 3,137 Male workers	N = 400 OR = 2.09 (1.40-3.14)	≥6 months working between 1:00-2:00 AM - Interviews	Smoking, alcohol, BMI, farming, occupational physical activity
Papantoniou *et al* (2015) [53]	Case-control $N_{controls}$ = 1,388 GP	N_{cases} = 1,095 OR = 1.14 (0.94-1.37) OR = 1.37 (1.05-1.81)	≥1 year night-shift work Interview ≥28 years night-shift work - Interview	Age, education, BMI, smoking, history of prostate cancer, sleep duration, sleep problems, chronotype, physical activity, diet habits
Dickerman *et al* (2016) [50]	Cohort N = 11,370 Older Finnish Twin Cohort	N = 602 HR = 1.3 (1.1-1.6)	Rotating shift work - Questionnaire	Age, education, BMI, physical activity, social class, smoking status, alcohol use, snoring, and zygosity
Behrens *et al* (2017)[45]	Cohort N = 1,757 Men from industrialized area in Germany	N = 76 HR = 2.29 (1.43-3.67) HR = 2.27 (1.42-3.64)	- Interview Ever shift work Ever night-work	Age, smoking status, family history of prostate cancer, education, and equivalent income
Åkerstedt *et al* (2017)[56]	Cohort N = 12,322 Men from the Swedish Twin Registry	N = 454 HR = 0.91 (0.74-1.12) HR = 0.72 (0.50-1.05)	- Interview Ever night-work Ever shift work	Age, educational level, tobacco use, alcohol; physical activity, body mass index, have children, coffee use, and previous cancer

[a]: effect (95% CI); GP: general population; OR: odds ratio; RR : risk ratio; OC: oral contraceptive; PMH: postmenopausal hormone; BMI: Body Mass Index; HRT: hormone replacement therapy; NSAID: nonsteroidal anti-inflammatory drugs; IUD: intrauterine device; ULF: Sweden's annual survey of living conditions; SIR: standardized incidence ratio.

Scores from the NOS to assess the risk of bias ranged from six to nine stars with an average of 7.5. Most case-control studies defined and selected groups adequately (30 of 33, 90.9%) and ensured comparability (28, 84.8%). One study obtained only one of the three maximum stars in the definition of the outcome or exposure (Table 3).

Table 3. Quality assessment of the studies following the Newcastle-Ottawa Scale

Case-control studies									
Author (Year)	Selection (Max. 4 stars)				Comparability (Max. 2 stars)	Exposure (Max. 3 stars)			Total Quality Score
	Case definition	Representativeness	Selection of control	Definition of control		Ascertainment of exposure	Same methods	None response rate	
Davis (2001)	*	*	*	*	**	(-)	*	(-)	7
Hansen (2001)	*	*	*	*	**	(-)	*	(-)	7
Schernhammer (2005)	*	*	(-)	(-)	*	*	*	*	6
Lie (2006)	*	*	(-)	*	**	(-)	*	(-)	6
O'Leary (2006)	*	*	*	(-)	**	(-)	*	*	7
Pesch (2010)	*	*	*	*	**	(-)	*	(-)	7
Lie (2011)	*	*	(-)	*	**	*	*	(-)	7
Hansen and Stevens (2012)	*	*	(-)	*	**	*	*	*	8
Hansen and Lassen (2012)	*	*	*	(-)	**	*	*	(-)	7
Fritschi (2013)	*	*	*	*	*	*	*	(-)	7
Grundy (2013)	*	*	*	*	**	*	*	(-)	8
Menegaux (2013)	*	*	*	*	**	*	*	*	9
Rabstein (2013)	*	*	*	*	**	(-)	*	(-)	7
Li (2015)	*	*	*	*	**	*	*	*	9
Papantoniou (2015)	*	*	(-)	*	**	(-)	*	*	7
Wang (2015)	*	*	(-)	*	**	*	*	*	8
Papantoniou (2016)	*	*	(-)	*	**	*	*	*	8

Cohort studies									
Author (Year)	Selection (Max. 4 stars)				Comparability (Max. 2 stars)	Outcome (Max. 3 stars)			Total Quality Score
	Representativeness of exposed	Selection of non-exposed	Ascertainment of exposure	Outcome of interest not present		Ascertainment of outcome	Follow-up	Adequacy of follow-up	
Schernhammer (2001)	*	*	(-)	(-)	*	*	*	*	6
Kubo (2006)	*	*	*	*	**	*	*	*	9
Schernhammer (2006)	*	*	*	*	**	(-)	*	*	8
Pronk (2010)	*	*	*	*	**	*	*	*	9
Kubo (2011)	*	*	*	*	**	*	*	*	9
Parent (2012)	*	*	*	*	**	*	*	*	9
Schwartzbaum (2007)	*	*	*	(-)	**	*	*	*	8
Knutsson (2013)	*	*	*	(-)	*	*	*	(-)	6
Koppes (2014)	*	*	*	*	**	(-)	*	*	8
Akerstedt (2015)	*	*	*	(-)	**	*	*	(-)	7
Travis (2016)	*	*	*	*	**	*	*	*	9
Dickerman (2016)	*	*	*	*	**	(-)	*	*	8
Vistisen (2017)	*	*	*	(-)	**	*	*	(-)	7
Wegrzyn (2017)	*	*	*	*	**	(-)	*	*	8
Behrens (2017)	*	*	*	(-)	**	*	*	(-)	7
Åkerstedt (2017)	*	*	*	(-)	**	*	*	(-)	7

Breast cancer was the principal focus of the selected works with 26 of them (78.8%) targeting breast cancer and night-shift work; most of them studied these factors in a sample population of nurses working in rotation shifts. Other occupations considered were armed forces[63] and textile industry [41], apart from the general population (Table 2).

One study revealed that higher urinary melatonin levels are associated with a lower risk of breast cancer[43], while another found that LAN and lack of sleep was associated to breast cancer, suggesting a link with melatonin levels[64]. GENICA[35,65] is a population-based case-control study on breast cancer with detailed information on shift work characteristics that reported association between long-term night-work and increased breast cancer risk, particularly of those ER-negative[35].

Women working at least three nights per month were defined as night-shift workers by the NHS studies[37,40,43], which reported a direct relationship between number of years of shift-work and risk of breast cancer: after 12 years of follow up, women who had worked at least 20 years on rotating night-shifts suffered more cases of breast cancer[66,67].

It is noteworthy that many of these studies found an association between night-shift work and breast cancer in long-term exposures[33,36,37,39,40,44,46-49,55,60-62] where long-term exposure was defined as a duration of at least 20 years; this indicates the long time required to see the effects of LAN exposure.

In spite of this apparent consensus regarding the association between night-shift work and breast cancer risk, there were other studies that found no relati-

oship[34,38,41,42,54,57]. Some authors point out that this could possibly be due to the relevance of menopausal status as a determining factor and the number of pre-menopausal and post-menopausal women in the sample population. Another limitation is the heterogeneity of rotating shifts, in other words, the frequency and number of consecutive night-shifts, which depend on the legislation in each country. Travis *et al*[54] analyse three different cohorts of women (Million Women Study, EPIC-Oxford, and UK Biobank). Joining the three cohorts, they recruited more than 790,000 women, and found that explosive to night-shift work (assessed as <10 years, 10-20 and >20) has no influence on breast cancer risk.

Despite the selected studies differing in design, study population, and conclusion, 76.0% of them found a significant association between breast cancer risk and night-shift work, although all of them acknowledged that further research is necessary to confirm this finding.

Eight publications studying night-shift work and prostate cancer were also reviewed[45,50-53,56] and six out of them (75.0%) found a significant association. One of them was a prospective cohort study of Japanese working men[52] that, by using Cox proportional-hazards model, concluded that, in comparison to day workers, rotating-shift workers were at greater risk of prostate cancer, while fixed night-work was associated with a small and non-significant increase in prostate cancer risk. The other study that observed a significant association between shift work and prostate cancer was a case-control study that evaluated the chronotype by logistic regression analysis adjusted for potential confounders[53], a significant increasing risk of prostate cancer was observed for night-shift work, being the highest risk in those who worked for 28 or more years (OR = 1.4; 95% CI: 1.1-1.8). Parent *et al*[58] conducted a case-control study with data from job histories from Quebec (Canada) between 1979 and 1985, comparing men who worked at night at some point to those men who never worked at night; the adjusted OR of prostate cancer for men who ever worked at night was 2.09 (95%CI: 1.40-3.14).

Kubo *et al*[51] observed some increase in the risk of prostate cancer for shift workers, although, as authors indicated, it was not statistically significant probably due to the small number of cases. However, Dickerman *et al*[50] suggest that chronotype may be associated with increased prostate cancer risk (HR 1.3; 95 % CI: 1.1-1.6) and having some influence on the relationship between shift work and prostate cancer risk.

The two most recent prostate cancer publications reached opposing conclusions: Behrens *et al*[45] reported an increased risk for prostate cancer in men in both long-term shifts or night-work (although it was higher within long-term shift workers) while Åkerstedt *et al*[56] concluded that working at night does not seem to constitute a risk factor for prostate cancer.

DISCUSSION

This systematic review included thirty-three studies that assessed the association between night-shift work and breast or prostate cancer. All the included studies found that there was a positive association between circadian disruption and cancer, although in some of them the association was non-significant, either for breast[33-35,38,41,42,44,47,54-57,63,65] or for prostate cancer[50-53,56,59]. According to NOS, the included studies had low risk of bias, given that 90.3% of them scored more than seven stars.

A possible relationship between exposure to light at night and breast cancer risk was first hypothesized in 1987[68]. However, whereas there is strong evidence of this association in studies on animals[7-9], in humans there is less evidence. There are numerous studies on the association between rotating shift work and general health that were not included in this review because they focused on chronic diseases (mainly cardiovascular risk factors) other than cancer[69]. Consistent with the current results, a 2014 meta-analysis of breast cancer risk and circadian disrup-

tion stemming from night-shift work, light at night, and sleep deficiency[29] concluded that there was a significant association between these circadian disruption factors and cancer in women (pooled RR = 1.14; 95% CI: 1.08-1.21). Nevertheless, the meta-analysis did not find an association between night-shift work and breast cancer incidence in particular[54].

An apparent difficulty is that shift work is not an easy concept to define[15,70] and it has not been described consistently across studies. Although most studies describe night-shift work as the shift beginning after 19:00 and ending before 09:00h, it is considerably more difficult to define rotating shift work. LAN is another factor involving circadian disruption that has been frequently examined[71-75]. Exposure to LAN is associated with many night-shift jobs; however, because there are many types of shift work, it is difficult for epidemiological questionnaires to cover all contingencies. Due to this heterogeneity, and in order to avoid confounding factors, these studies were excluded from this review.

Various publications analysed night-shift work and breast cancer risk from a genetic perspective. They were based on the hypothesis that circadian clock gene variants modulate breast cancer risk. The results of these studies showed an association between several polymorphisms in circadian genes, night-work, and breast cancer risk[76-78]. Although the biological mechanisms participating in carcinogenesis based on circadian disruption are not clear, some studies point out that nighttime work may cause abnormalities in the circadian clockwork and may lead to failures in the control of the cell division cycle as well as a predisposition to certain diseases, such as non-Hodgkin lymphoma[79].

Furthermore, shift work is also associated with certain metabolic, physiologic, and behavioural factors[10] which are difficult to isolate from sleep loss and circadian disruption. For example, some studies reported that, in comparison to non-shift workers, shift workers showed higher percentages of cigarette smoking and alcohol consumption[37,44,47,80]; such factors may act as confounders distorting the results as they are also related to higher cancer risk.

Because of the relatively small number of studies on the link between night-shift work and cancer, evidence of the association of these factors is limited. Besides, the heterogeneous nature of the research examined in this review means that the results should be interpreted with caution. The studies also differed in their population samples, definitions of shift work, exposure duration, length of follow-up, study design (retrospective/prospective), and control variables. Although such heterogeneity provides a wider scope and a broader view of the issue, it also means that the conclusions are far from being conclusive. For example, a crucial factor as exposure duration, is irregularly presented and differently considered in the studies, not only concerning whether it is a permanent night-shift work or a rotating shift, but also the number of hours of rotating night-shift work and the frequency of night-shift per week/month/year. In spite of this research provides some evidence that night-shift work produces an effect in long-term exposures (after 20-30 years), findings pertaining to short-term exposures are somewhat less consistent.

Exposure itself is also very differently presented. Depending on the study, the assessment of this variable may be based on the following factors: sleep loss, circadian disruption, shift work, night-shift work, napping, etc. Different studies used divergent definitions of shift work; thus, both studies that found a positive association as well as those that did not, may have experienced some difficulty in pooling the frequencies of night-shifts due to the inexistence of fixed criteria regarding the number of night-shifts (per week/month/year) required for long-term circadian disruption. Due to all these reasons, a quantitative summary of the results was not feasible and a qualitative summary was done instead.

Five recent reviews and meta-analyses in breast cancer have produced discrepant results, with some of them finding an association between night-shift work and elevat-

ed breast cancer risk[29,30,81,82], while others found little or no effect on breast cancer incidence[12,54]. In addition, one of these meta-analyses included studies of airline cabin crew even though the increased cancer risk in this occupational group (by 48.0%) could stem from exposure to cosmic radiation[81]. Nonetheless, in long-distance flights, potential circadian rhythm disturbances may be related to exposure to LAN and jet lag. That type of epidemiological studies was not included in our review because circadian disruption was no directly related to shift work in cabin crew.

The number of participants could be another determining factor in the studies reviewed because it is far from easy to find people who have worked rotating night-shifts for 20 or more years. The pre/post-menopausal status of female participants should also be considered since this is another important risk factor for breast cancer, as postmenopausal women can be more exposed to hormones through oestrogen replacement therapy, in addition to their increased age[83]. Other limitation of our review was that the sample population in many studies on shift work and breast cancer risk consisted solely of nurses; the majority of these studies, exception made by the more recent ones[34,54], reported a higher risk of breast cancer in women working on night-shifts for long periods. However, this association might be affected by confounding factors, such as alcohol and smoking habits, previously mentioned.

Given the difficulties in measuring the effect of shift work on cancer risk, and given the confounding factors and different population samples, our judgment is that there is no definitive epidemiological evidence yet that circadian disruption leading to increased cancer risk.

Despite the increasing number of studies publishing on breast and prostate cancer risk in relation to night-shift work, melatonin levels, and circadian rhythm, the evidence of a possible association remains inconclusive due to both limitations inherent to this type of studies and differences in the aetiology of cancers. Clearly, more epidemiological research is needed in order to draw definitive conclusions on the impact of circadian disruption on human health and its possible association with increased cancer risk. Meanwhile, it is advisable to follow the precautionary principle recommended by the IARC in 2007.

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